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REVIEW ARTICLE

Role, Regulation and Reception of Association of Brain and Diabetes: Emerging Evidences and Contemporary Insights

Dr. Vijay Negalur[a], Dr. Benny Negalur[b]

a Honorary Professor,Rajiv Gandhi Medical College(RGMC), Thane, Maharashtra, India, Email: negalur@msn.com

b Associate Professor,Terna Medical College,Nerul,Navi Mumbai, Maharashtra, India bennynegalur@gmail.com

Historical Perspectives

Hyperglycaemic states can be produced experimentally by certain defined neural stiumuli or lesions. This was first demonstrated by Claude and Bernad in 1849 who induced hyperglycaemia and glycosuria in anaesthetised animals by puncture (piqure) of the floor of the fourth ventricle. Despite this important discovery, it took approximately 150 years before significant efforts aimed at understanding the underlying mechanism of brain-mediated control of glucose metabolism were made. Long sustained hyperglycaemia lasting for hours, has been produced in unanesthetized cats, rabbits, and rats by injection into the cerebral ventricles or the cisterna magna of a variety of drugs. The drugs which have induced such prolonged hyperglycaemia include - morphine, etorphine, pethidine, beta-endorphin, enkephalin, bombesin, TRH, cholecystokinin, naloxone, propranolol, phentolamine, chloralose, magnesium chloride and GABA. These drugs probably act at the ventral surface of the brainstem and initiate a sympathetic discharge to the adrenals which results in a prolonged release of relatively small amounts of adrenaline. When adrenaline is released in this way hyperglycaemia may be the only effect. The mechanism of the piqûre hyperglycaemia of Claude Bernard may be the same, although Bernard assumed that it resulted from an effect on the floor of the fourth ventricle, i.e. on the dorsal surface of the brainstem. However, it is clear from his description that his trochar not only pricked the floor of the fourth ventricle but penetrated to the ventral surface of the brainstem.

Similarly, neurogenic hyperglycaemia was produced in cats by decerebration by Mellanby in 1919. A series of experiments conducted by Donhoffer and Macleod for the nervous control of carbohydrate metabolism demonstrated that decerebration of rabbits under Amytal or luminal anaesthesia produced hyperglycaemia if the pons was involved. Also, they had observed that in rabbits with low initial levels of glycogen the hyperglycaemias could not be accounted for solely based onglycogenolysis. In these animals, double adrenalectomy or administration of atropine and section of both the vagus nerves prevented

hyperglycaemia from developing after decerebration. However, in rabbits, with high preoperative levels of glycogen, decerebration at the level of pons did induce hyperglycaemia.

Release of adrenaline from the adrenals is usually regarded as a stress response, as in fight, flight, fear, or rage when it is suddenly released in large amounts and produces its typical cardiovascular and ocular reactions. The results now obtained with drugs injected intraventricularly or intracisternally suggest an additional physiological role for adrenaline when it is released over prolonged periods and in relatively small amounts producing only hyperglycaemia. Such a release may play a role in the day-to-day control of blood glucose, and its disturbance might underlie non-insulin-dependent diabetes.

Technological developments allowing for genetically-mediated manipulation of selected molecular pathways in a neurone-type-specific fashion unravelled the importance of specific molecules in specific neuronal populations. These neuronal pathways govern glucose metabolism in the presence and even in the absence of insulin. Also, a peculiarity of these pathways is that certain biochemically-defined neurones govern glucose metabolism in a tissue-specific fashion.[1,2]

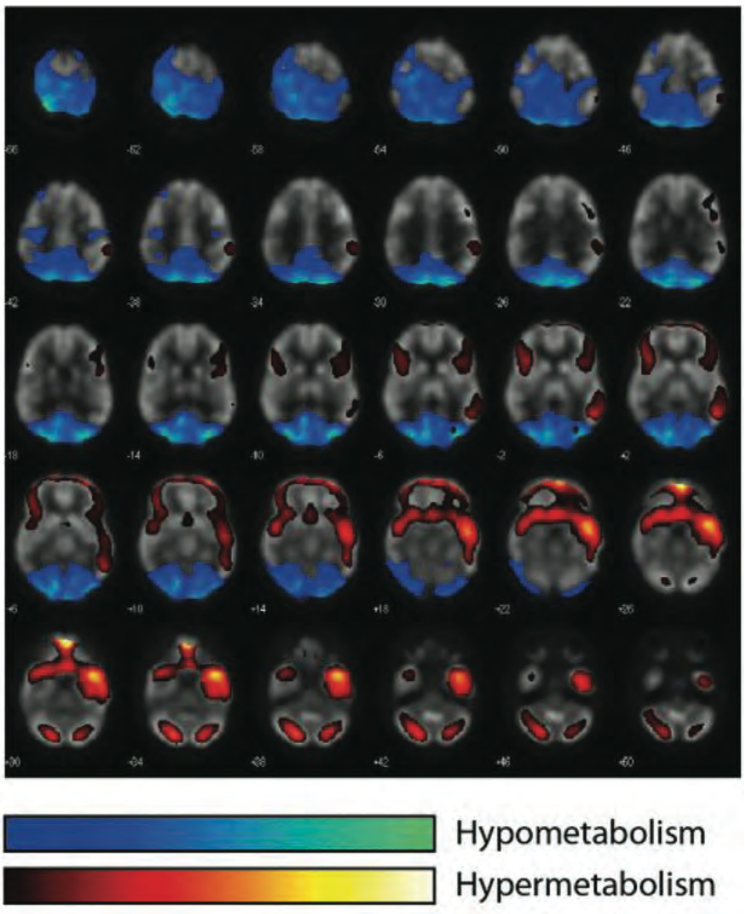
Glucose: the major fuel for the brain

The hypothalamus contains specialized glucose sensing neurons which are scattered throughout the nuclei controlling distinct neuroendocrine functions. These neurons play a key role in enabling the hypothalamus to partition energy to meet these peripheral survival needs without endangering the brain's glucose supply. Hypothalamic glucose sensing neurons were discovered in the 1960s, and there is evidence that they play a role in maintaining cerebral glucose levels.[3]

The peripheral energy status regulates glucose sensitivity. For example, during energy deficit such as fasting specific hypothalamic glucose sensing neurons become sensitized to decreased glucose. This increases the gain of the information relay when glucose availability is a greater concern for the brain. Finally, there are changes in glucose sensitivity under pathological conditions (e.g. recurrent insulin-hypoglycaemia, diabetes).

The tight regulation of glucose metabolism is critical for brain physiology. Consistent with its critical role for physiological brain function, disruption of normal glucose metabolism as well as its interdependence with cell death pathways forms the pathophysiological basis for many brain disorders.[4]

Figure 1 depicts an example of a diagnostic [^{18}F] fluoro-2-deoxyglucose PET-CT.
Figure 1. Example of a diagnostic [^{18}F] fluoro-2-deoxyglucose PET-CT



In a 23-year-old female patient after a 2-month course of severe anti-NMDA-R encephalitis, typically showed widespread frontotemporal cortical hypermetabolism as well as bioccipital and cerebellar cortical hypometabolism.

Adapted from: Mergenthaler P. Sugar for the brain: the role of glucose in physiological and pathological brain function *Trends Neurosci* 2013 Oct; 36(10):587–97.

Therefore, it would not be wrong to call the brain as a 'selfish brain' atleast for the fact that the glucose is the primary fuel of the brain. Thus, it is essential to maintain adequate levels for brain function at all times.

The mammalian brain depends upon glucose as its main source of energy, and tight regulation of glucose metabolism is critical for brain physiology. Consistent with its critical role for physiological brain function, disruption of normal glucose metabolism as well as its interdependence with cell death pathways forms the pathophysiological basis for many brain disorders.

Role of glucose for brain function

Glucose is the main source of energy for the brain. Its few uses are as follows:

(a) Specialised centres in the brain, including proopiomelanocortin (POMC) and agouti-related peptide (AgRP) neurons in the hypothalamus, sense central and peripheral glucose levels and regulate glucose metabolism through the vagal nerve as well as neuroendocrine signals.

(b) Glucose supply to the brain is regulated by neurovascular coupling and may be modulated by metabolism-dependent and -independent mechanisms. Glucose enters the brain from the blood by crossing the blood-brain barrier (BBB) through glucose transporter 1 (GLUT1).

(c) Glucose and other metabolites (e.g. lactate, Lac) are rapidly distributed through a highly coupled metabolic network of brain cells.

(d) Glucose provides the energy for neurotransmission.

(e) Several glucose-metabolising enzymes control cellular survival. Disturbed glucose metabolism on any of these levels can be the foundation for the development of a large variety of disorders of the brain.

Cellular distribution of the principal GLUTs in the nerves and blood vessels

Mechanisms of regulation of glucose transport from blood to brain that involve differential distribution of the BBB glucose transporter in subcellular compartments of brain capillary endothelial cells. The BBB in vivo is situated at the level of the endothelia in brain microvessels and functions to

Figure 2. The role of glucose for brain metabolism.

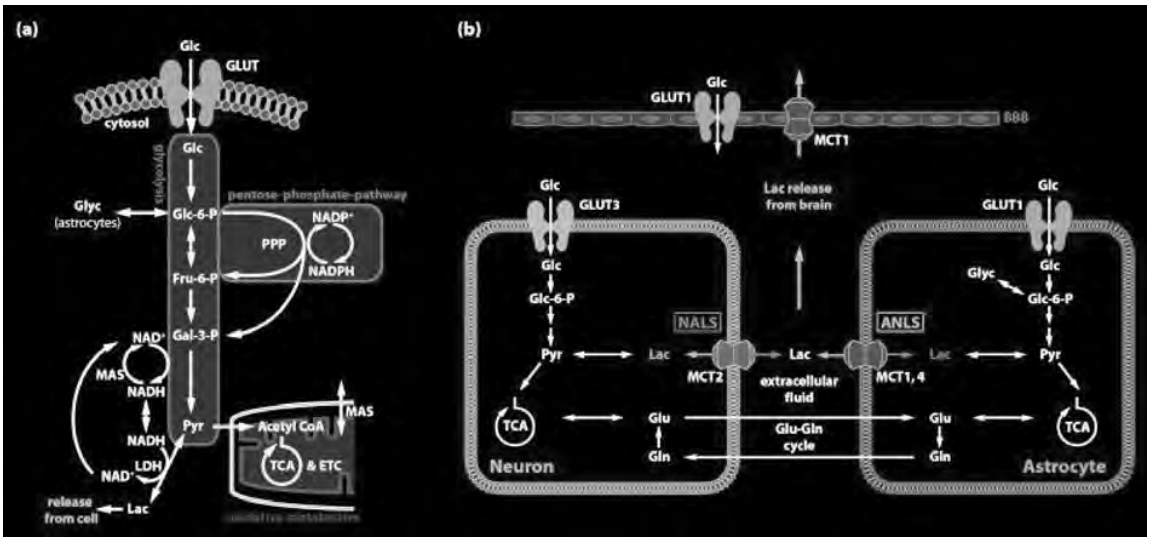


Figure 3. Generation of energy in brain and three models for the fate of lactate derived from glucose metabolism in the brain.

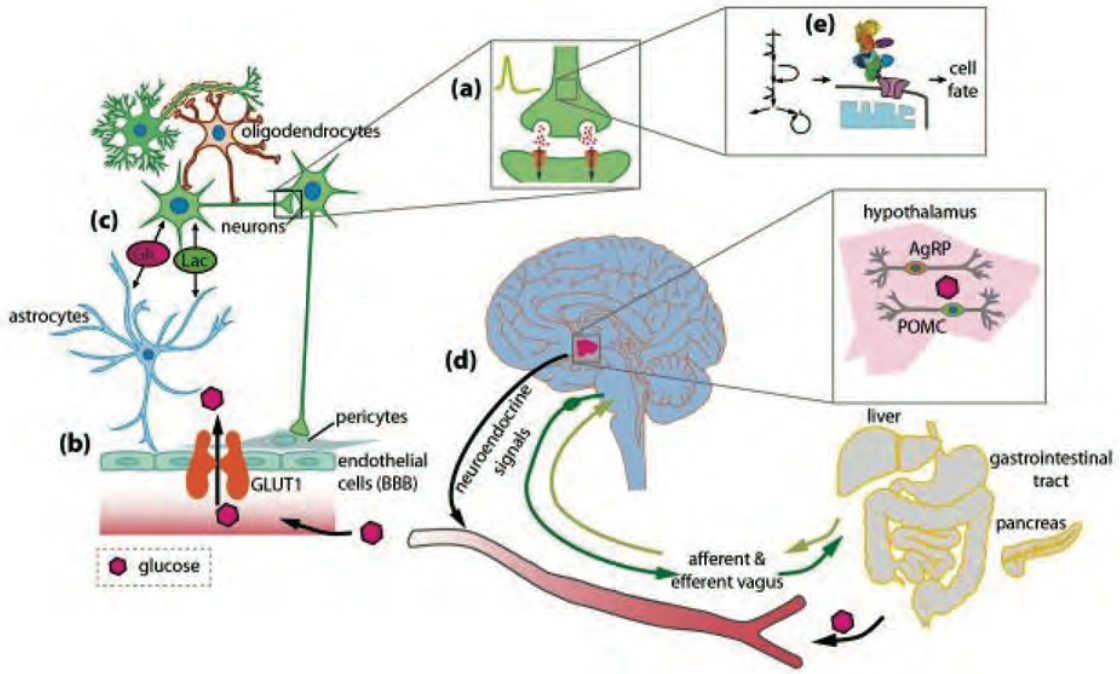
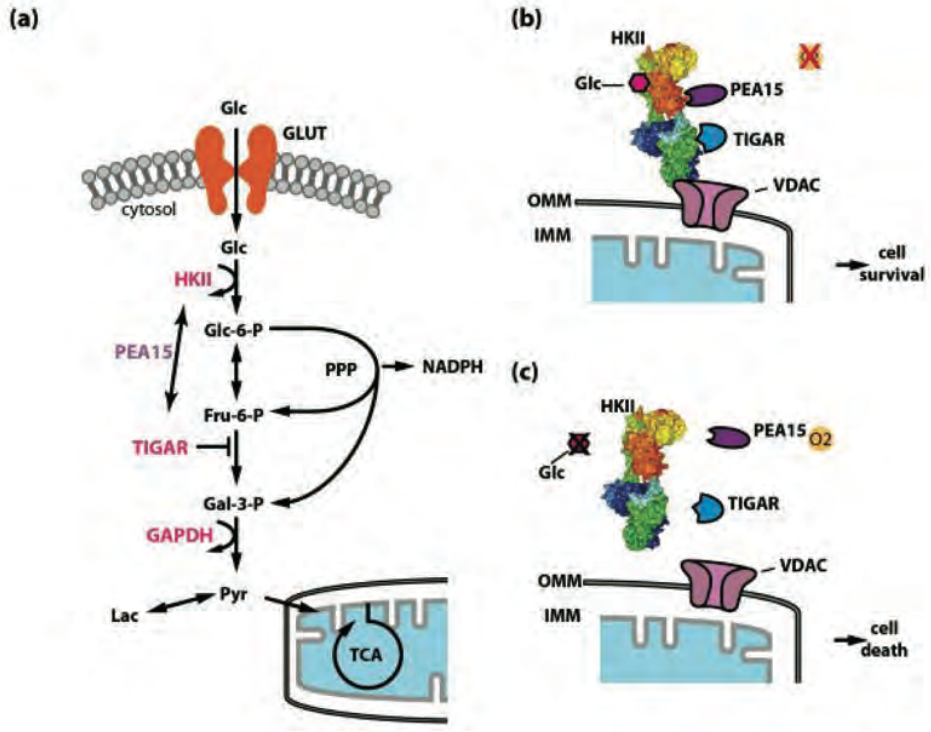


Figure 4. The connection between glucose metabolism and cell death.



regulate the composition of the extracellular milieu of brain. There is a symmetric distribution of the glucose transporter on the lumenal and ablumenal membranes of the brain capillary endothelial cell that makes up the BBB in vivo

However, the presence of brain endothelial tight junctions allows for asymmetric distribution of BBB plasma membrane proteins. Studies suggest that[5,6]

1. GLUT-1 is asymmetrically distributed on the BBB plasma membrane with an approximately 4-fold greater abundance on the ablumenal membrane as compared to the lumenal membrane;
2. Approximately 40% of the endothelial glucose transporter protein is contained within the cytoplasmic space, which provides a mechanism for rapid up-regulation of the transporter by altered distribution of transporter between cytoplasmic and plasma membrane compartments and
3. No significant labeling of neuropil is found with antisera directed against the GLUT-1 protein.

The patterns of hypoglycaemic encephalopathy on diffusion-weighted imaging (DWI) and the relationship between the imaging patterns and clinical outcomes have been evaluated through MR imaging techniques. The retrospective analysis demonstrate that white matter was more sensitive to hypoglycaemia than previously thought and there was no specific association between the patterns of injury and clinical outcomes whether the cerebral cortex, deep gray matter and/or white matter were affected. Diffuse and extensive injury observed on the DWI predicts a poor neurologic outcome in patients with hypoglycaemic injuries.[7]

Clinically, in the real world scenario Type 1 diabetes has been the benchmark for the evaluation of the relationship for the poor glycaemic control and the nerve conduction defects. Adolescents with type 1 diabetes receiving modern multiple insulin injection therapy (MIT) have abnormal EEGs, and to elucidate possible correlations with a history of severe hypoglycaemia, poor metabolic control and nerve conduction defects. Pronounced abnormalities in the temporal regions may not be related to these risk factors.[8]

Interestingly, there is a strong connection between the neurons in the brain and the retina. Glucose availability and visual functions are related. The glucose is stored in the retina, specifically in the glial Müller cells and supplied upon demand. Human positron emission tomography studies indicate increased blood flow and glucose metabolic rate in primary visual cortex during stimulation, with retinotopic distribution. Retinal electrophysiology co-varies with glucose concentration in vitro models as well as in humans, at comparable concentrations in the physiological range. K-channels regulated by intracellular ATP are thought to link neuron excitability (and electrophysiological activity) on the metabolic state. High-affinity sulphonylurea binding sites for K-channels are widely distributed in brain. K-channels conceivably modulate neurotransmitter release and are inactivated by elevated glucose concentrations and sulfonylurea drugs used to treat diabetes.[9]

Brain is insulin sensitive

Brain has been identified as an insulin-sensitive organ. Evidence demonstrates that insulin action in the brain produces multiple behavioural and metabolic effects, influencing eating behaviour, peripheral metabolism, and cognition. Modern neuroimaging methods have provided new means of probing brain insulin action, revealing the influence of insulin on both global and regional brain function. Moreover, the disturbances in brain insulin action can be observed in obesity and type 2 diabetes, as well as in aging and dementia.

The most prominent factors associated with brain insulin resistance, include obesity, T2D, genes, maternal metabolism, normal ageing, inflammation, and dementia, and on their roles regarding causes and consequences of brain insulin resistance. There are specific beneficial effects of enhanced brain insulin signalling on human eating behaviour and cognition.[10]

Brain is the New Pancreas

Brain contains insulin concentrations which are several folds higher than the blood plasma levels.

Insulin in the brain regulates the metabolism, molecular composition, and cognitive performance of microcircuits and reduces food intake; cerebral insulin levels are altered in diabetes, ageing, obesity, and Alzheimer's disease. Experimental evidence demonstrates that the insulin is strongly expressed in GABA ergic neurogliaform cells in the cerebral cortex of the rat detected by single-cell digital PCR. Focal application of glucose or glibenclamide to neurogliaform cells mimics the excitation suppressing the effect of external insulin on local microcircuits via insulin receptors. Thus, neurogliaform cells might link GABAergic and insulinergic action in cortical microcircuits.[11] The disturbances in the brain insulin system lead to central insulin resistance, which is one of the primary causes of type 2 diabetes mellitus, metabolic syndrome, and Alzheimer's disease. The insulin signalling system of the brain has a key role in the regulation of fundamental cell processes in neurons and controls metabolic processes in the CNS and periphery. In hypothalamic neurons insulin signalling system interacts closely with the other signalling systems regulated by leptin, melanocortin peptides, dopamine, serotonin, and is the key component of the hypothalamic signalling network, which integrates and transforms the central and peripheral signals.[12]

Brain as insulin sensitive tissue

Over the past few years, evidence has accumulated that the human brain is an insulin-sensitive organ. Insulin regulates activity in a limited number of specific brain areas that are important for memory, reward, eating behaviour, and the regulation of whole-body metabolism. Accordingly, insulin in the brain modulates cognition, food intake, and body weight as well as whole-body glucose, energy, and lipid metabolism. However, brain imaging studies have revealed that not everybody responds equally to insulin and that a substantial number of people are brain insulin resistant. Factors associated with brain insulin resistance include factors such as obesity and increasing age, as well as possible pathogenic factors such as visceral fat, saturated fatty acids, alterations at the BBB and certain genetic polymorphisms.[13]

Hypothalamic Targets of Insulin and Leptin Action

The brain is now regarded as an insulin-sensitive organ with widespread, yet selective, expression of the insulin receptor in the olfactory bulb, hypothalamus, hippocampus, cerebellum, amygdala, and cerebral cortex.

Importantly, recent advances in modern neuroimaging techniques, such as functional magnetic resonance imaging (fMRI) or magnetoencephalography (MEG), have made it possible to investigate the action of insulin in the brain in humans, providing new insights into the pathogenesis of brain insulin resistance and obesity. fMRI studies have shown a significant insulin-induced attenuation predominantly in the occipital and prefrontal cortical regions and the hypothalamus, successfully localising insulin-sensitive brain regions in healthy, mostly normal-weight individuals. Further, research need to be focussed on the efforts to localise brain areas affected by insulin resistance in obese individuals, which is an important prerequisite for selectively targeting brain insulin resistance in obesity. Insulin receptor signalling in the brain is important for neuronal development, glucoregulation, feeding behaviour, body weight, and cognitive processes such as with attention, executive functioning, learning, and memory. Emerging evidence has demonstrated insulin receptor signalling to be impaired in several neurological disorders. Moreover, insulin receptor signalling is recognised as important for dendritic outgrowth, neuronal survival, circuit development, synaptic plasticity, and postsynaptic neurotransmitter receptor trafficking.[14] Mainly known for its role in peripheral glucose homeostasis, insulin has also significant impact within the brain, functioning as a key neuromodulator in behavioural, cellular, biochemical, and molecular studies.[15,16]

Leptin and insulin, two anorectic hormones, have key roles in the regulation of body weight and energy homeostasis, as highlighted by the fact that several obese patients develop resistance to these hormones. Within the brain,

the hypothalamic proopiomelanocortin and agouti-related protein neurons have been identified as major targets of leptin and insulin action.

The discovery of the adipocyte hormone leptin and the demonstration that severe obesity in ob/ob and db/db mice results from mutation of genes encoding leptin and its receptor, respectively. Substantial progress has been made in understanding brain mechanisms of leptin action, translating this knowledge into more effective treatment of obesity remains an elusive goal.[17]

Novel incretin analogues cross the BBB and show physiological activity and neurogenesis in the brain, which may be of use as a treatment of neurodegenerative diseases. Type 2 diabetes is a risk factor for Alzheimer's disease (AD), most likely linked to an impairment of insulin signalling in the brain. Therefore, drugs that enhance insulin signalling may have therapeutic potential for AD. Liraglutide (Victoza) and exenatide (Byetta) are novel long-lasting analogues of the GLP-1 incretin hormone and are currently available to treat diabetes. They facilitate insulin signalling via the GLP-1 receptor (GLP-1R). Numerous in vitro and in vivo studies have shown that GLP-1 analogues have a range of neuroprotective properties. GLP-1 Rs are expressed in the hippocampal area of the brain an important site of adult neurogenesis and maintenance of cognition and memory formation.[18]

Future directions and emerging pathways

Brain is being explored from a human evidence perspective. There are numerous ongoing clinical studies which is an attempt to scrutinise the impact of diabetes (both type 1 and type 2) on the functional domain of brain. These include the assessment of the impact of circulating glucose levels upon the brain responses; a study is underway which utilises MRI to access the structural and functional rehabilitation in the cerebral infarction patients with diabetes; the relationship between the dietary glycaemic index, brain function and food intake in patients with type 1 diabetes; assessment of cerebral responses to insulin-induced hypoglycaemia.[19]

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